Stratton VA Medical Center
IRB Standard Operating Procedure: Research Involving Vulnerable Populations

Department of Veterans Affairs (VA) regulations at 38 CFR 16.111(b), Food and Drug Administration (FDA) regulations, and the Common Rule require IRB(s) to give special consideration to protecting the welfare of particularly vulnerable participants, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB ensures that it has adequate representation on the Board to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

a. **Elements IRB(s) Consider in Reviewing Research Involving Vulnerable Participants.** The IRB pays special attention to specific elements of the research plan when reviewing research involving vulnerable participants.

(1) Strategic issues include inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.

(2) The IRB carefully considers group characteristics, such as economic, social, physical, and environmental conditions to ensure that the research incorporates additional safeguards for vulnerable participants.

(3) Investigators should not be permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research participants merely because they are a readily available “captive” population.

(4) The IRB is knowledgeable about applicable state or local laws that bear on the decision-making abilities of potentially vulnerable populations. State statutes often address issues related to competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent and the waiver of parental permission for research.

(5) Just as in providing medical care, research studies that plan to involve any potentially vulnerable population must have adequate procedures in place for assessing and ensuring participants' capacity, understanding, and the ability to give informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable participants, the IRB reviews and verifies that such procedures are part of the research plan. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable participants. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a participant advocate, interpreter for hearing-impaired participants, translation of informed consent form with HIPAA provisions or separate HIPAA consents into languages the participants understand, and reading the consent form to participants slowly and ensuring their understanding paragraph by paragraph.

(6) The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent form with HIPAA provisions or separate HIPAA consent to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

b. **Pregnant Women, Fetuses, and Human in Vitro Fertilization**. The Department of Health and Human Services (DHHS) regulations at 45 CFR Part 46, Subpart B detail special protections for research involving pregnant women, fetuses, or human in vitro fertilization. Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent. *In general, the Stratton VAMC IRB does not review research in this category. See pg 8, 'Checklist for Determining the Status of Sub Part B Criteria for Research with Pregnant Women.' The IRB will use this checklist in the event that research with pregnant women is performed at Stratton VAMC.*

c. **Research Involving Prisoners.** DHHS regulations at 45 CFR 46, Subpart C detail special protections for research involving prisoners, who due to their incarceration may have a limited ability to make truly voluntary and un-coerced decisions about whether or not to participate as participants in research. *In general, the Stratton VA IRB does not review research in this category.*

d. **Research Involving Children.** The VA is authorized to care for veterans and to conduct research that enhances the quality of health care delivery

to veterans. VA policy stipulates that children cannot be included in VA-approved research unless a waiver has been granted by the Chief Research and Development Officer (VA Directive 2001-028, dated April 27, 2001).

DHHS regulations at 45 CFR 46, Subpart D require special protections for research involving children. Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted.

There is three main issues to consider when reviewing research involving children: (1) risk-benefit analysis, (2) parental permission, and (3) assent of the child. In general, the Stratton VA IRB does not review research in this category.

e. **Research Involving Decisionally Impaired Participants.** Decisionally impaired persons are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affect cognitive or emotional functions. Other individuals, who may be considered decisionally impaired with limited decision-making ability are individuals under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps.
Impaired decision-making capacity may fluctuate. Principal investigators should consider this in the informed consent process. There are no regulations specific to research involving cognitively impaired persons. However, there are specific VA policies that require certain findings to be made before persons incompetent to consent may be enrolled in research with the permission of a surrogate.

In all cases, the IRB takes special care to consider issues such as the selection of participants, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. Decisions should be made with the utmost deference to the ethical principles underlying human participants research as set forth in *The Belmont Report*. Capacity should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. In cases where research involving cognitively impaired individuals is approved, the IRB should require additional safeguards (e.g., involvement of participant advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants.
The PI or designee uses the IDMC Screening tool to evaluate all potential subjects.

f. **Surrogate Permission with Participants Judged Incompetent to Consent.** A research participant must be competent to give informed consent; otherwise, the consent of the legally authorized representative of the patient must be obtained. Participants deemed incompetent include children, legal minors, and the mentally disabled. If competency issues are anticipated for a study, they must be acknowledged in the research proposal and the procedures used to evaluate competency must be described in detail. VA policy (Cooperative Studies Program Guidance) limits the conditions under which consent from legally authorized representatives (i.e., surrogate consent) can be obtained in lieu of consent from the participant. VA policy (VHA Handbook 1200.5) recognizes as legally authorized representatives:

(1) Persons appointed as health care agents under a Durable Powers of Attorney for Health Care (DPAHC).
or
(2) Court appointed guardians
and
(3) Next of kin in the following order: spouse, adult child, parent, and adult sibling, and adult grandchild.

Surrogate consent may be used only when the prospective participant is incompetent as determined by two VA physicians, after appropriate medical evaluation, and there is little or no likelihood that the participant will regain competence within a reasonable period of time, or as established by legal determination. This definition of incompetence is not limited to the legal definition but may also be a clinical judgment that a person lacks the capacity to understand the circumstances of participating in research and to make an autonomous decision to take part.

This policy is designed to protect patients from exploitations harm and, at the same time, make it possible to conduct essential research on problems that are unique to patients who are incompetent (e.g., a study of treatment options for comatose patients can only be done with incompetent participants).

Before incompetent persons may be involved in any VA research, the IRB must find and document in writing that the proposed research meets all of the following conditions:

(1) <u>Only incompetent persons are suitable.</u> Competent persons are not suitable for the proposed research. The investigator must demonstrate that there is compelling reason to include incompetent persons as participants. Incompetent persons must not be involved as participants simply because they are readily available.

(2) Favorable Risk/Benefit Ratio. The proposed research entails no significant risk, or if the research presents risk of harm then there must at least be a greater probability of direct benefit to the participant than of harm. Incompetent people will not be participants of research that imposes a risk of injury, unless that research is intended to benefit the participant and the probability of benefits is greater than the probability of harm.

(3) Voluntary Participation. Participants do not resist participating. Under no circumstances may participants be forced or coerced into participating. Participants may not be forced to participate even if the surrogate consent is obtained.

(4) Well-Informed Representatives. Procedures have been devised to ensure that participants' representatives (appointed under Durable Powers of Attorney for Healthcare, and next of kin or guardians) are well informed regarding their roles and obligations to protect the rights and welfare of the participants they represent. Representatives must be informed in writing that their obligation is to try to determine what the participant would do if competent, or if the participant's wishes cannot be determined, what is in the participant's best interests.

The IRB must review and approve a surrogate consent form.

Consultation may be sought from the Chief of Service or Physician Executive. Consultation should also be obtained from psychiatry, if based on a diagnosis of mental illness.

g. **Research Involving Other Potentially Vulnerable Adult Participants.** Employees, students, and trainees in the VA Medical Center should also be considered vulnerable participants. Thus, the IRB upholds the same standards in approving research involving these groups as other vulnerable participants research. Special precautions must be taken to avoid coercion or the appearance of coercion when including students/trainees/ employees in research. Similarly, it is important to avoid the appearance of any special treatment or any penalty of individuals in these categories based on their decision to participate or not to participate in a research protocol. Finally, confidentiality of data may be of special concern to these classes of research participants.
The context of the research is an important consideration for the IRB to have in mind when reviewing research that involves other potentially vulnerable participants. Research involving homeless persons, members of particular minority groups, or the economically or educationally disadvantaged pose significant challenges. Research involving significant follow-up procedures or offering significant monetary compensation may

unduly influence certain types of participants, and IRB takes such considerations into account. Nevertheless, research involving these participants is socially important for understanding and eventually improving adverse health in these populations.

h. **Human Fetal Tissue Transplantation Research.** Public Law 103-43 governs human fetal tissue transplantation research supported by DHHS. In general, the VAWNYHS does not review research in this area.

i. **Participation of Non-Veterans.** Research involving non-veterans may be approved by the IRB if there are insufficient veterans available to complete the study, all regulations pertaining to veterans pertain to non-veterans and there is provision for payment for research related injury.

j. **Critical Care Research.** The IRB recognizes the difficulty in obtaining informed consent in the Critical Care setting since the participant's medical status may preclude the ability of the participant to provide informed consent. However, when the research presents no more than minimal risk of harm to participants, and involves no procedures for which written consent is normally required outside the research context, the IRB may waive the requirement for written consent (CFR 21, 56.109(c)). In cases where a informed consent form with HIPAA provisions or separate HIPAA consent is required, all attempts must first be made to determine what the participant would do if competent. In cases where a consent is required, the following procedures (in sequential order) should be followed in attempting to obtain consent by participants unable to provide consent in the critical care setting:

(1) Endeavor to obtain informed written consent from the legally-authorized representative/next-of-kin after attempting to explore what they believe the participant would do if competent and what they think is in the incompetent person's best interest.

(2) Obtain consent from legally authorized representative/next-of-kin by telephone.

(3) As a last resort, the informed consent form with HIPAA provisions or separate HIPAA consent can be signed by the Chair of the Critical Care Committee or his/her designee, provided they are not associated with the study, have evaluated the patient, are fully informed with respect to the study, and have read the consent form.

A statement should be made on the informed consent form with HIPAA provisions or separate HIPAA consent explaining the circumstances under which the participant's (or next-of-kin's) signature was not obtained.

k. **Research with prisoners of war (POW) is prohibited.**
The organization is aware of the definition of “prisoner of war” for the Department of Defense component granting the addendum.

l. **Other Considerations**

- A non-therapeutic clinical trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written consent document.
- Non-therapeutic clinical trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

  a) The objectives of the trial cannot be met by means of a trial in subjects who can give consent personally.
  b) The foreseeable risks to the subjects are low. The negative impact on the subject’s well-being is minimized and low.
  d) The trial is not prohibited by law.
  e) The opinion of the IRB is expressly sought on the inclusion of such subjects, and the written opinion covers this aspect.

  *Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

Checklist for Determining the Status of Sub Part B Criteria for Research with Pregnant Women:

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.